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Declaration under Rule 4.17:

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27 May 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: DIAGNOSTICS AND THERAPEUTICS FOR DISEASES ASSOCIATED WITH GROWTH HORMONE SECRETAGOGUE RECEPTOR (GHS)

(57) Abstract: The invention provides a human GHS which is associated with the cardiovascular diseases, disorders of the peripheral and central nervous system, respiratory diseases like COPD and asthma, hematological diseases, cancer, gastro-intestinal diseases and inflammation. The invention also provides assays for the identification of compounds useful in the treatment or prevention of cardiovascular diseases, disorders of the peripheral and central nervous system, respiratory diseases like COPD and asthma, hematological diseases, cancer, gastro-intestinal diseases and inflammation. The invention also features compounds which bind to and/or activate or inhibit the activity of GHS as well as pharmaceutical compositions comprising such compounds.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/02688

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 G01N33/68 G01N33/566 C12Q1/68 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/092292 A (BEDNAREK MARIA ;MERCK & CO INC (US)) 6 December 2001 (2001-12-06)	1-12, 19-21, 24-26
Y	pages 5-10; claim 12; examples 2,3	22,23
X	BEDNAREK ET AL: "Structure-Function Studies on the New Growth Hormone-Releasing Peptide, Minimal Sequence of Ghrelin, and its Role for Activation of Growth Hormone Secretagogue Receptor 1a" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 43, no. 23, 26 October 2000 (2000-10-26), pages 4370-4376, XP002166937 ISSN: 0022-2623 the whole document	1-12, 19-21, 24-26

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 November 2003

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INTERNATIONAL SEARCH REPORT

International Publication No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>BODART V ET AL: "IDENTIFICATION AND CHARACTERIZATION OF A NEW GROWTH HORMONE-RELEASING PEPTIDE RECEPTOR IN THE HEART"</p> <p>CIRCULATION RESEARCH, GRUNE AND STRATTON, BALTIMORE, US,</p> <p>vol. 85, no. 9,</p> <p>29 October 1999 (1999-10-29), pages 796-802, XP001006287</p> <p>ISSN: 0009-7330</p> <p>the whole document</p>	18-26
X	<p>KATUGAMPOLA SIDATH D ET AL:</p> <p>"(125I-His9)-ghrelin, a novel radioligand for localizing GHS orphan receptors in human and rat tissue; up-regulation of receptors with atherosclerosis"</p> <p>BRITISH JOURNAL OF PHARMACOLOGY,</p> <p>vol. 134, no. 1, September 2001 (2001-09), pages 143-149, XP002259571</p> <p>ISSN: 0007-1188</p> <p>the whole document</p>	1,4,8,9, 18,26
X	<p>KATUGAMPOLA S D ET AL: "From gene to function: recently adopted orphan receptor for the vasodilator peptide ghrelin is up-regulated in human atherosclerotic coronary artery."</p> <p>BRITISH JOURNAL OF PHARMACOLOGY,</p> <p>vol. 134, no. Proceedings Supplement,</p> <p>November 2001 (2001-11), page 29P,</p> <p>XP008023924</p> <p>Meeting of the British Pharmacological Society; Dublin, Ireland; July 03-05, 2001</p> <p>ISSN: 0007-1188</p> <p>abstract</p>	1,4,8,9, 18,26
X	<p>NAGAYA N ET AL: "Hemodynamic and hormonal effects of human ghrelin in healthy volunteers."</p> <p>AMERICAN JOURNAL OF PHYSIOLOGY. REGULATORY, INTEGRATIVE AND COMPARATIVE PHYSIOLOGY. UNITED STATES MAY 2001,</p> <p>vol. 280, no. 5, May 2001 (2001-05), pages R1483-R1487, XP002259572</p> <p>ISSN: 0363-6119</p>	12-17,26
Y	<p>page R1486 - page R1487; figures 2,3</p>	22,23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/02688

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: -
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery: claims 2-3
Rule 39.1(iv) PCT - Diagnostic method practised on the
2. ☒ Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-26 (in part)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: -

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery: claims 2-3

Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body: claim 18

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy: claim 26

Continuation of Box I.2

Claims Nos.: -

Present claims 1-26 relate to diseases defined by reference to a characteristic or property, namely to involve the cardiovascular system. Present claims 19, 20 and 24-26 furthermore relate to compounds defined by reference to a desired characteristic or property, namely to bind to or modulate the activity of the type 1a growth hormone secretagogue receptor (GHS receptor).

The claims cover all diseases and compounds having said characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such diseases and compounds. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the diseases and compounds by reference to a result to be achieved

The search was therefore restricted to the following subject-matter:

cardiovascular diseases referred to in claims 1-26: heart failure, myocardial infarction, ischemic diseases, arrhythmias, hypertensive vascular diseases, peripheral vascular diseases and atherosclerosis (as defined on pages 55-57 of the description).

compositions referred to in claims 19, 20 and 24-26: ghrelin analogues, antibodies and antisense polynucleotides.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: claims 1-26 (in part)

Therapeutic and diagnostic use of GHS receptor for cardiovascular diseases

2. claims: claims 1-26 (in part)

Therapeutic and diagnostic use of GHS receptor for disorders of the peripheral nervous system

3. claims: claims 1-26 (in part)

Therapeutic and diagnostic use of GHS receptor for disorders of the central nervous system

4. claims: claims 1-26 (in part)

Therapeutic and diagnostic use of GHS receptor for respiratory diseases

5. claims: claims 1-26 (in part)

Therapeutic and diagnostic use of GHS receptor for haematological diseases

6. claims: claims 1-26 (in part)

Therapeutic and diagnostic use of GHS receptor for cancer

7. claims: claims 1-26 (in part)

Therapeutic and diagnostic use of GHS receptor for gastrointestinal diseases

8. claims: claims 1-26 (in part)

Therapeutic and diagnostic use of GHS receptor for inflammation

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/02688

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0192292	A	06-12-2001	CA 2411667 A1	06-12-2001
			EP 1353683 A2	22-10-2003
			WO 0192292 A2	06-12-2001

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